Published in final edited form as:

J Consult Clin Psychol. 2014 December ; 82(6): 1049–1059. doi:10.1037/a0037401.

Stable Remission and Recovery after Acute Phase Cognitive Therapy for Recurrent Major Depressive Disorder

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Abstract

Objective—Continuation phase cognitive therapy (C-CT) or fluoxetine (FLX) reduces relapse in adults with major depressive disorder (MDD; Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013). Among patients at higher risk for relapse, we hypothesized that continuation phase treatment reduces residual symptoms and facilitates stable remission and recovery.

Method—Outpatients ($N=241$) with recurrent MDD who responded to acute-phase CT with higher risk for relapse (i.e., had unstable remission defined by any of the last 7 acute-phase Hamilton Rating Scale for Depression [Hamilton, 1960] scores ≥ 7) were randomized to 8 months of C-CT, FLX, or pill placebo and followed 24 additional months. Psychiatric Status Ratings (Keller et al., 1987) of 1 or 2 (absent or minimal depressive symptoms) for 6 and 35 continuous weeks post-randomization defined stable remission and recovery, respectively.

Results—Actuarial estimates of stable remission (97%) and recovery (94%) by the end of follow-up were high and did not differ among groups. Observed (unadjusted) proportions of

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Drs. Vittengl and Clark have no interests to disclose regarding this research. Dr. Thase has no conflicts of interest pertaining to this paper, although he does report the following relationships with companies that develop treatment for depression or provide education pertaining to those treatments: Dr. Thase has provided scientific consultation to Alkermes, Allergan, Astra-Zeneca, Bristol-Myers Squibb Company, Dey Pharma, L.P., Eli Lilly & Company, Forest Pharmaceuticals, Inc., Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Merck and Co. Inc., Neuronetics, Inc., Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, L.L.C., Pfizer (formerly Wyeth-Ayerst Pharmaceuticals), PgX, Inc., Shire US Inc., Sunovion Pharmaceuticals, Inc., Supernus Pharmaceuticals, Takeda (Lundbeck), Teva and Transcept Pharmaceuticals. Dr. Thase has received grant funding from the Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Eli Lilly & Company, Forest Laboratories, the National Institute of Mental Health, Otsuka Pharmaceuticals, PharmaNeuroboost, and Roche. He has equity holdings in MedAvante, Inc. and receives royalty income from American Psychiatric Foundation, Inc., Guilford Publications, Herald House, Oxford University Press, and W.W. Norton & Company. His wife is employed by Peloton Advantage, which does business with Pfizer. Dr. Jarrett's medical center receives the fees from the cognitive therapy she provides to patients. Dr. Jarrett is a paid consultant to the NIMH. Dr. Jarrett's medical center receives the fees from the cognitive therapy she provides to patients.

patients remitting (70%) and recovering (47%) before relapse or attrition were lower. During the continuation phase, C-CT ($d = 0.21$) and FLX ($d = 0.25$) patients had significantly lower mean depressive symptoms than controls, but C-CT and FLX patients did not differ from each other, nor did the three experimental groups differ during follow-up.

Conclusion—Many patients who responded to CT with higher relapse risk subsequently remitted and recovered after discontinuation of acute-phase treatment. After discontinuation, C-CT and FLX decreased levels of residual depressive symptoms, but neither significantly increased the likelihood of stable remission or recovery, beyond the moderate to high levels observed among patients who did not relapse.

Keywords

depression; cognitive therapy; fluoxetine; stable remission; recovery

Major depressive disorder (MDD) is a common, often recurrent, illness that produces significant disability and increased mortality (e.g., Vittengl & Jarrett, 2013). Because MDD is usually episodic, pharmacotherapies and psychotherapies are often staged by their treatment goals. Acute-phase treatments may produce initial response (i.e., substantial reductions in symptoms such that patients no longer meet criteria for MDD). After response, continuation-phase treatments aim to prevent relapse and recurrence (i.e., meeting MDD criteria before or after recovery, respectively) and to promote stable remission and recovery (e.g., weeks and months, respectively, of few or no symptoms). Finally after recovery, maintenance treatments may prevent recurrence and sustain recovery (e.g., Frank et al., 1991; Rush et al., 2006). Stable remission and recovery are distinguished conceptually as temporary abatement versus the end of an index major depressive episode, respectively. Consequently, stable remission and recovery are operationalized, respectively, as shorter or longer periods of minimal or absent depressive symptoms (e.g., 6 weeks and 8 months, in the current analyses). Relapse and recurrence are conceptualized in parallel as resurgence of an index depressive episode versus a new depressive episode, respectively.

Acute-phase cognitive therapy (CT; Beck et al., 1979) is a well-established, efficacious treatment for MDD. Roughly two-thirds of patients who complete acute-phase CT respond to the treatment (e.g., Craighead et al., 2007). Further, meta-analysis shows that acute-phase CT is superior to non-active control conditions (e.g., pill placebo) in reducing depressive symptoms ($d = 0.67$) and at least comparable to other depression-specific acute-phase treatments (e.g., pharmacotherapy and other psychotherapies; $d = 0.03$; Cuijpers et al., 2012). Nonetheless, many responders to acute-phase CT relapse or eventually suffer recurrent episodes, underscoring the need for continuation treatments. For example, although acute-phase CT reduces relapse compared to acute-phase pharmacotherapy discontinued after response, more than half of acute-phase CT responders will relapse within 2 years (e.g., Vittengl et al., 2007).

In this context, researchers have developed and tested continuation and maintenance forms of CT. For example, continuation phase CT (C-CT; Jarrett, 1989; Jarrett, Vittengl, & Clark, 2008) was associated with lower relapse in an initial cohort-control study (Jarrett et al., 1998) and in a randomized pilot study (Jarrett et al., 2000). Based on these results, Jarrett et

al. (2001) conducted a larger controlled trial in which responders to acute-phase CT were randomized to 8 months of C-CT ($n = 41$) or assessment-only control ($n = 43$) and followed 16 additional months. The 8-month relapse proportion among C-CT patients (10%) was significantly lower than among patients receiving only assessment (31%), and among the subset of patients with unstable remission in acute-phase CT (one or more Hamilton Rating Scale of Depression [HRSD; Hamilton, 1960] scores ≥ 7 during the final 6 weeks), C-CT significantly reduced relapse/recurrence over 24 months as well (37% vs. 62%; Jarrett et al., 2001). After response to acute phase pharmacotherapy, CT has also been shown to reduce relapse/recurrence more than clinical management (e.g., Fava, Rafanelli, Grandi, Conti, & Belluardo, 1998; Fava et al., 2004), more than naturalistic treatment as usual (e.g., Teasdale et al., 2000; Ma & Teasdale; Bondolfi et al., 2010), and comparably to continuing pharmacotherapy (e.g., Blackburn & Moore, 1997; Kuyken et al., 2008).

More recently, Jarrett et al. (2013) treated a large sample ($N = 523$) of outpatients with recurrent MDD using acute-phase CT. A subset of responders showed unstable remission during the acute phase, which placed them at higher risk for relapse and recurrence (Jarrett & Thase, 2010). To compare continuation-phase therapies, consenting higher-risk responders ($N = 241$) were randomized to 8 months of C-CT, fluoxetine (FLX), or pill placebo (PBO) and were subsequently followed 24 additional months. Jarrett et al. (2013) found that more patients relapsed in the PBO arm (33%) than the C-CT (18%) and FLX (18%) arms during the 8-month experiment. However, the relapse/recurrence estimates for C-CT (45%), FLX (41%), and PBO (56%) did not differ significantly across the full 32 months (8-month experiment plus 24-month follow-up). Use of potentially mood-altering non-protocol medications during the 32-month study was limited (i.e., about 15% of patients reported any use, mostly short-term) and also did not differ significantly among experimental groups. Thus, both C-CT and FLX reduced relapse comparably and significantly more than PBO, as long as treatment was active.

Although researchers have focused on reducing relapse and recurrence traditionally, stable remission and recovery are also important in defining successful outcomes for patients with MDD (e.g., Rush et al., 2006). Even patients without relapse and recurrence may experience sub-diagnostic residual symptoms that impair quality of life (e.g., Zimmerman, Posternak, & Chelminski, 2007). Stable remission and recovery, in contrast, are defined by sustained minimal or absent symptoms and mark better outcomes than the simple absence of major depression (e.g., Fava, Ruini, & Belaise, 2007). For example, in the previous clinical trial of 84 responders to acute-phase CT (including patients with both lower and higher risk of relapse) randomized to 8 months of C-CT or assessment-only control and followed 16 additional months (Jarrett et al., 2001), C-CT significantly increased recovery (62% vs. 84%) but not stable remission (88% vs. 97%) over 24 months (Vittengl, Clark, & Jarrett, 2009). As in the current analyses, stable remission and recovery were defined as 6 weeks and 8 months, respectively, of consistently minimal or absent depressive symptoms.

However, definitions of remission and recovery have varied widely in past research, and those definitions that allow higher symptom levels and measure shorter time periods are likely to yield larger proportions of MDD patients achieving remission and recovery (e.g., Dunlop et al., 2012). For example, prior definitions of remission and recovery have focused

on the absence of a major depressive episode, thus including patients with moderate, sub-diagnostic symptom levels (e.g., Beevers Rohde, Stice, & Nolen-Hoeksema, 2007; McCleod, Kessler, & Landis, 1992) rather than restricting positive outcomes to patients with minimal or absent depressive symptoms. Definitions have also included a single symptom assessment focusing on one time period (e.g., the past month to define remission; Furukawa et al., 2001; at the end of acute phase treatment to define recovery; Elkin et al., 1989) rather than repeated assessments to establish continuously-reduced symptoms. The current definitions of stable remission and recovery (continuously minimal or absent depressive symptoms for 6 weeks and 8 months, respectively; Jarrett & Thase, 2010), although arbitrary because there are no clear breaks in depressive symptom severity and duration continua, reflect increasing standards for treatments that produce prolonged wellness (Jarrett et al., 2001; Rush et al., 2006).

Although the primary focus of the current clinical trial was on prevention of relapse and recurrence, Jarrett and Thase (2010) also defined stable remission and recovery *a priori* as target outcomes reflecting “return to usual self” among patients with recurrent MDD. In this context, we extended Jarrett et al.'s (2013) analyses of higher risk responders to acute-phase CT randomized to 8 months of depression-specific continuation treatment (C-CT or FLX) or PBO and assessed 24 additional months. Randomized patients had no MDD and HRSD ≤ 12 at the end of acute-phase CT indicating response, but also HRSD ≥ 7 at one or more of the last 7 acute-phase assessments indicating higher relapse risk. We examined the proportions of these patients achieving stable remission and recovery at 8, 20, and 32 months post-randomization (i.e., at the end of experimental phase and after 1 and 2 years of follow-up). Although not specified as a primary outcome during the clinical trial's design (Jarrett & Thase, 2010), evolving research suggests that residual symptoms produce life-interference and increase relapse/recurrence risk making reduction of residual symptoms a central goal of continuation and maintenance treatments of MDD (e.g., Fava & Tomba, 2010; Zajecka, Kornstein, & Blier, 2013). In this context, we analyzed continuous residual symptom levels to provide additional information about the gradations of patients' longitudinal outcomes, including symptoms experienced after remission, recovery, relapse, and recurrence. We tested the hypotheses that depression-specific continuation treatments (C-CT and FLX) produce significantly (a) more stable remission and recovery than PBO and (b) lower weekly depressive symptom scores than PBO. Psychiatric Status Ratings (Keller et al., 1987) of 1 or 2 (absent or minimal depressive symptoms) for 6 and 35 continuous weeks post-randomization defined stable remission and recovery, respectively. To our knowledge, the current trial is the first to compare stable remission, recovery, and continuous symptoms among higher-risk responders to acute-phase CT randomized to C-CT, FLX, and PBO, and so may help guide clinical practice.

Method

Participants

Data are from a clinical trial comparing relapse/recurrence among acute-phase CT higher risk responders ($N = 241$) randomized to continuation-phase CT, FLX, or pill PBO (see Jarrett & Thase, 2010, and Jarrett et al., 2013, for additional detail). Outpatients who (a)

provided written informed consent; (b) met *DSM-IV* criteria for recurrent MDD (American Psychiatric Association, 2000); (c) previously had remitted between depressive episodes, had at least one prior episode with complete inter-episode recovery, or had antecedent dysthymic disorder; and (d) scored ≥ 14 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) participated.¹ Patients who (a) had severe or poorly controlled concurrent medical disorders that could cause depression, (b) had psychotic or organic mental disorders, bipolar disorder, active substance dependence, or primary obsessive-compulsive or eating disorders, (c) could not complete questionnaires in English, (d) were an active suicide risk, (e) were <18 or >70 years old, (f) had not responded previously to ≥ 8 weeks of CT or 6 weeks of fluoxetine, or (g) were pregnant or planned to become pregnant during the first 11 months after intake were excluded. The Structured Clinical Interview for *DSM-IV* (First, Spitzer, Gibbon, & Williams, 1996) was used for diagnosis. Randomized patients were $M = 43$ ($SD = 12$) years old and had completed $M = 16$ ($SD = 3$) years of education; 67% were women; 85% were white, 8% black, and 8% other races/ethnicities. Patients' age of MDD onset was $M = 21$ ($SD = 10$) years, their current major depressive episode had lasted $M = 24$ ($SD = 44$) months. At study intake, participants had experienced a minimum of 2 (median = 4; 25-75th percentile range 3-5) major depressive episodes, including the intake episode.

Acute Phase

A total of 523 unmedicated adults provided informed consent and were eligible to begin the acute-phase CT protocol. The acute-phase CT protocol lasted 12 weeks; up to 2 additional weeks were permitted for rescheduling. Patients received 2 CT sessions per week for 4 weeks, after which those who showed $\geq 40\%$ reduction in HRSD scores received 8 additional weekly sessions (16 total sessions), whereas patients who showed $< 40\%$ reduction in HRSD scores received 4 additional weeks of twice-weekly sessions before beginning weekly sessions (20 total sessions).² The higher "dose" of CT provided to patients with less early improvement was provided to increase their chance of response. Responders were patients who--by independent evaluation--had no major depressive episode and HRSD ≤ 12 at the end of acute-phase CT. Patients were stratified by *a priori* criteria for stable/unstable remission into lower (the last 7 acute-phase HRSD scores all ≤ 6 ; $n = 50$) and higher risk (at least one of the last 7 acute-phase HRSD scores ≥ 7 ; $n = 242$) groups. Higher risk patients (i.e., patients eligible for randomization to continuation treatments) were identified at the end of the acute phase.

Continuation Phase

All but 4 acute-phase CT responders judged to be at higher risk accepted randomization to the 8-month continuation-phase therapies, including C-CT ($n = 86$) or clinical management with either FLX ($n = 86$) or PBO ($n = 69$).³ A blinded evaluator assessed patients at the end

¹Due to a scoring error, 2 patients erroneously entered acute phase CT with HRSD = 13 at one of two diagnostic visits. During CT, one of these patients responded and one dropped out. As recommended by the Data Safety and Monitoring Board (DSMB), and as analyzed in a previous publication examining relapse and recurrence (Jarrett et al., 2013), the two patients are analyzed here as they were treated during data collection.

²Four (1 early and 3 late) responders were misclassified as late and early responders, respectively. As recommended by the DSMB, they are analyzed here as they were treated during data collection.

of months 4 and 8 (and in between if relapse was suspected) for *DSM-IV* MDD with the SCID (First et al., 1996) and Longitudinal Interval Follow-up (Keller et al., 1987) Psychiatric Status Ratings (PSR). After relapse, patients were referred for treatment.

The C-CT protocol included 10, 60-minute sessions (4 biweekly then 6 monthly sessions) (Jarrett, Vittengl & Clark, 2008). C-CT patients applied learned coping skills to residual and emergent depressive symptoms; generalized CT skills across problems, time, and situation; and practiced preemptive coping to identify cognitive and behavioral risks. Patients' acute-phase and C-CT therapists were the same, with few exceptions (e.g., due to a therapist's maternity leave). The 16 cognitive therapists were doctoral- or masters-level professionals who had completed at least 1 year of supervised CT training. Before treating protocol patients, therapists demonstrated competence in CT by maintaining Cognitive Therapy Scale (Young & Beck, 1980) scores > 40 and by site supervisors' judgment. Throughout the study, therapists received ongoing supervision or consultation. Experienced faculty members led weekly group supervision sessions and were available for case consultation. Supervision groups watched videotapes of randomly selected CT sessions, rated them using the Cognitive Therapy Scale, and provided feedback to therapists.

The clinical management protocol (Fawcett et al., 1987) was provided by experienced pharmacotherapists and included 10 sessions (up to 45 minutes for session 1 and 30 minutes for sessions 2-10) scheduled with the same frequency as C-CT. Pharmacotherapists were prohibited from using any specific methods of C-CT. At each site, research pharmacies dispensed active FLX or identical PBO capsules. Patients first received 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, and 40 mg/day thereafter in the double-blinded protocol. Pharmacotherapists were allowed to decrease doses to lessen patients' side effects, but patients who could not tolerate at least 10mg/day were removed from medication and received only clinical management. Most patients (73%) achieved 40mg/day of FLX or PBO (Jarrett et al., 2013).

Follow-up Phase

Patients completing the continuation phase entered a 24-month follow-up. With the same procedures as in the continuation phase, blinded evaluators assessed patients every 4 months. Patients experiencing depressive symptoms were also encouraged to contact study staff for an interim evaluation. In the event of relapse or recurrence, patients were referred for treatment.

Measure

Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987). Independent evaluators completed this semi-structured retrospective interview every 4 months post-acute-phase CT, at study exit, and when patients, therapists, or follow-up evaluators suspected major depressive relapse or recurrence. Additional evaluations at suspected

³Three non-responders were randomized in error. As recommended by the DSMB, they are analyzed here as they were treated during data collection. Also, during the final years of randomization, allocation to PBO was greatly reduced to increase the proportions of patients randomly assigned to the two depression-specific treatments. At intake to acute-phase CT, mean HRSD scores did not differ significantly among patients who were later randomized to C-CT, FLX, or PBO. Similarly at randomization, mean HRSD scores did not differ among randomized groups, $ps > .50$.

relapse/recurrence were uncommon (1 patient in C-CT, 6 in FLX, and 3 in PBO). The LIFE includes weekly psychiatric status ratings (PSR) of *DSM-IV* MDD ranging from 1 (no symptoms) to 6 (meets MDD criteria with severe impairment and/or psychosis). Potentially mood-altering non-protocol treatment was tracked with the LIFE, as well, and coded as present or absent during each week. Reliability and validity of the PSR in the current clinical trial (Jarrett & Thase, 2010) is supported by the median lag 1 autocorrelation ($r = .87$), which shows moderately high consistency in symptom ratings from week to week, and by the convergence of PSR with concurrent HRSD scores from regularly scheduled masked evaluations (median $r = .66$, range .34-.74), which shows moderately high agreement in symptom levels across instruments.

Outcome Definitions

We measured stable remission, recovery, and continuous symptom levels using PSR for MDD from the LIFE. Defined *a priori* (Jarrett & Thase, 2010), PSR values of 1 (no symptoms) to 2 (one or two mild symptoms) for 6 and for 35 continuous weeks defined stable remission and recovery, respectively. PSR values of 3 (obvious symptoms with moderate impairment) and 4 (major symptoms and impairment) mark noteworthy but sub-diagnostic symptomatology. PSR values of 5 (meets full MDD criteria) to 6 (meets MDD criteria with severe impairment and/or psychosis) for 2 weeks defined relapse and recurrence when they occurred before and after recovery, respectively. Patients who relapsed/recurred were referred for treatment outside of the experimental protocol at that time (Jarrett & Thase, 2010). Consequently, patients who relapsed first were coded as not achieving stable remission and/or recovery and were censored from analyses of stable remission and recovery at the time of relapse. Finally, the full range of PSR values from 1 to 6 measured continuous symptom levels throughout the continuation and follow-up study phases (139 weekly ratings).

Statistical Analyses

Our first hypothesis concerned the proportions of patients who remitted and recovered differing across experimental groups (C-CT, FLX, PBO). We employed two complementary methods to estimate proportions of patients remitting and recovering. First, we tallied the observed proportions of patients known to have remitted and recovered at three *a priori* time points, the end of the experimental phase plus 1 and 2 years after the end of the experimental phase (i.e., 8, 20, and 32 months after randomization, respectively). We compared these proportions using Pearson chi-square tests. Because some patients were censored before observed stable remission and recovery due to dropping from the study and/or relapsing, the observed proportions may underestimate the true proportions of patients who remitted and recovered (e.g., Allison, 2010). Consequently, we also used Cox regression, a type of time-to-event or “survival” analysis that incorporates censoring information to provide adjusted, actuarial estimates of stable remission and recovery that are generally regarded as more accurate (e.g., Singer & Willett, 2003). The Cox regressions used event status (1 = achieved, 0 = did not achieve, stable remission and recovery) and time to the event, which was operationalized as weeks since randomization until the event or until censoring. Patients were censored at the earliest of (a) the end of the study (139 weeks after randomization), (b) when they dropped out of the study, or (c) when they relapsed before achieving stable

remission or recovery. In the regressions, we predicted time to events from randomized assignment (C-CT, FLX, or PBO) and included all randomized patients. Cox regression assumes that time-to-event curves are parallel across groups. This proportional hazards assumption was not rejected for stable remission or recovery models, $ps > .25$, based on Kolmogorov-type supremum tests in SAS software version 9.3 (SAS Institute, Inc., Cary, NC), supporting the validity of statistical tests based on the time-to-event curves. Further, outcomes of Cox regression tests were unchanged when using score and Wald chi-square tests in place of the likelihood ratio chi-square tests reported in the Results.

Our second hypothesis concerned weekly symptom intensity scores (PSR) differing among experimental groups (C-CT, FLX, PBO). We tested this hypothesis using repeated-measures multilevel models, also known as random coefficient or hierarchical linear models. The models included up to 139 weekly PSR scores per patient. Multilevel models allowed retention of cases with some missing data (as opposed to exclusion of cases with any missing data in ordinary least squares ANOVA) due to dropping out of the study, and flexibility in modeling the within-subjects covariance structure to produce better parameter estimates and more powerful hypothesis tests (e.g., Littell, Milliken, Stroup, & Wolfinger, 1996; Nich & Carroll, 1998). Instead of censoring patients at the point of relapse, we controlled non-protocol treatment as a covariate and used all available symptom data including observations after relapse or recurrence. A lag-1 autoregressive error structure fit the data better than other common patterns (e.g., compound symmetric, Huyhn-Feldt), as judged by Bayes Information Criterion, and was retained for hypothesis tests. For significant results, we computed effect size d as the difference in least-squares estimated means divided by the SD for the full sample of PSR observations.

Results

Observed Proportions of Patients with Stable Remission and Recovery

Table 1 shows the raw proportions of patients observed to have remitted and recovered by three time points, the end of the experimental phase plus 1 and 2 years after the end of the experimental phase (i.e., 8, 20, and 32 months after randomization, respectively). Patients who relapsed first were coded as not achieving stable remission or recovery. By the end of the study (32 months post-randomization), the majority of patients were observed to have remitted ($168/241 = 70\%$; 95% CI 63-75%) and nearly half recovered ($113/241 = 47\%$; 95% CI 40-53%). The C-CT, FLX, and PBO conditions did not vary significantly in observed proportions of patients remitting or recovering at 8, 20, or 32 months after randomization. However, observed proportions of patients with stable remission and recovery may underestimate actual proportions because some patients were censored due to relapse (after which they were referred for treatment outside of the experimental protocol) and dropping from the study before remission ($72/241 = 30\%$; 95% CI 24-36%) and before recovery ($128/241 = 53\%$; 95% CI 47-60%). Figure 1 shows the flow of patients among these outcomes.

Relations of Observed Stable Remission and Recovery with Relapse and Recurrence

Stable remission and recovery differed empirically from the absence of relapse and recurrence (see Figure 1). Minus patients who dropped out before an event (relapse, recurrence, stable remission, or recovery), nearly all patients who failed to remit (26/27 = 96%; 95% CI 81-100%) and/or recover (30/31 = 97%; 95% CI 83-100%) relapsed. Further, 32% (54/168; 95% CI 25-40%) of patients who remitted later relapsed or recurred, and 21% (24/113; 95% CI 14-30%) of patients who recovered later recurred. Only 1 patient (1/241 = 0.4%; 95% CI 0-2%) maintained moderate depressive symptoms, staying between full MDD symptoms (relapse and recurrence) and sustained minimal or absent symptoms (stable remission and recovery) throughout the 32-month study. In sum, negative outcomes (relapse and recurrence) were uncorrelated with stable remission, $r = -.03$ (95% CI $-.16, .09$), and correlated modestly but statistically significantly with recovery, $r = -.24$ (95% CI $-.35, -.12$). However, the timing of events highlighted the episodic nature of MDD--not achieving positive outcomes (remission and recovery) strongly predicted return of major depression, but achieving positive outcomes did not guarantee freedom from return of major depression (see Figure 1).

Estimated Proportions of Patients with Stable Remission and Recovery

We used Cox regression analysis to estimate the proportions of patients remitting and recovering, and to compare time to stable remission and recovery among the three groups (C-CT, FLX, PBO), taking into account censoring of patients who relapsed or dropped out of the study before stable remission and/or recovery (see Table 2). All randomized patients ($N = 241$) were included in these analyses. By the end of the 32-month study, estimates of the proportions of patients remitting (97%) and recovering (94%) were high, after adjusting for patients censored before these events. In the time-to-event analyses, stable remission and recovery did not vary significantly among C-CT, FLX, and PBO at 8, 20, or 32 months after randomization. Figures 2 and 3 show stable remission and recovery curves and censoring for the three treatment groups.

Early in the experiment, more patients were censored before stable remission and recovery due to relapses and drops in PBO, and to a lesser extent in FLX, compared to CCT (see Figures 2 and 3).⁴ For example, by 3 months post-randomization, the proportions of patients censored before stable remission (14/86 = 16% in C-CT; 21/86 = 24% in FLX; 26/69 = 38% in PBO), $\chi^2(2) = 9.33, p < .01$, and recovery (16/86 = 19% in C-CT; 22/86 = 26% in FLX; 27/69 = 39% in PBO), $\chi^2(2) = 8.32, p = .02$, varied significantly among groups. By 32 months, the rank order of groups in censoring was maintained for stable remission (22/86 = 26% in C-CT; 23/86 = 27% in FLX; 28/69 = 41% in PBO), $\chi^2(2) = 4.87, p = .09$, and recovery (42/86 = 49% in C-CT; 43/86 = 50% in FLX; 43/69 = 62% in PBO), $\chi^2(2) = 3.31, p = .19$, but the differences were reduced to non-significant levels. Differences between depression-specific treatments (especially C-CT) and PBO in stable remission and recovery may be underestimated because of the greater censoring in PBO early in the experiment.

⁴After 6 weeks, the proportions of patients censored before remission and recovery differed because some patients were censored after remission and before recovery.

Comparisons of Stable Remission and Recovery with a Previous Clinical Trial

It is also possible that patients in the PBO group, who also received clinical management, benefitted to some extent relative to the group who received only assessment (i.e., no treatment) in the previous trial (Vittengl et al., 2009). We tested this possibility by comparing the current CCT ($n = 86$) and PBO ($n = 69$) group results to published results for C-CT ($n = 41$) and assessment-only control ($n = 43$) in the previous randomized trial (Vittengl et al., 2009). The previous trial ended at 24 months post-randomization, so we used Cox regression to estimate stable remission and recovery proportions at the 24-month time point in the current trial. We compared proportions between trials using two-tailed z -tests. In the C-CT cells, the current study's stable remission estimate of 94% was very similar to 97% estimated in the previous trial ($z = 0.74$, $p = .46$), and the current recovery estimate of 91% also was comparable to the 84% recovery estimate in the previous trial ($z = 1.07$, $p = .28$). Similarly, stable remission in PBO in the current trial of higher risk CT responders (94%) was slightly but not significantly higher than stable remission in assessment control in the previous trial of both higher and lower risk CT responders (88%), $z = 1.07$, $p = .29$. However, there was evidence that recovery in higher risk responders randomized to PBO (79%) was more frequent than recovery in higher and lower risk responders randomized to assessment control in the previous trial (62%), $z = 2.00$, $p < .05$. Moreover, recovery in the current C-CT group (91%) exceeded recovery in the previous trial's assessment control group (62%), $z = 3.89$, $p < .01$.

Continuous Symptom Scores

All available data, including observations after events (relapse, recurrence, remission, and recovery), were included in analyses of continuous symptom scores, and non-protocol treatment was controlled. Averaging across 139 weekly observations (32 months) after acute-phase CT response, mean PSR suggested mild depressive symptoms ($M = 1.85$, $SD = 1.12$), and an average of 3.9% of patients received potentially mood-altering non-protocol treatment each week. Figure 4 shows weekly mean PSR estimated in a repeated-measures multilevel model. When time was blocked into three periods defined *a priori* (continuation phase, follow-up years 1 and 2), the non-protocol treatment covariate, $F(1, 21 \times 10^3) = 1.64$, $p = .20$, and the main effect of protocol continuation phase treatment were not significant, $F(2, 485) = 0.23$, $p = .80$; but the main effect of period, $F(2, 14 \times 10^3) = 12.53$, $p < .01$, and the protocol treatment-by-period interaction were significant, $F(4, 14 \times 10^3) = 5.73$, $p < .01$. Pair-wise tests showed that symptoms decreased from the continuation phase ($M = 2.00$, $SE = 0.04$) to the first year of follow-up ($M = 1.88$, $SE = 0.04$), $d = 0.11$, $p < .01$, two-tailed, and again from the first to second ($M = 1.80$, $SE = 0.04$) follow-up year, $d = 0.07$, $p = .02$, two-tailed. Further, both C-CT ($M = 1.93$, $SE = 0.07$; $d = 0.21$, $p = .03$, two-tailed) and FLX ($M = 1.90$, $SE = 0.07$; $d = 0.25$, $p = .01$, two-tailed) had significantly lower symptoms than PBO ($M = 2.17$, $SE = 0.08$) during the continuation phase, but did not differ from each other, and none of the groups differed during the first (C-CT $M = 1.90$, $SE = 0.07$; FLX $M = 1.89$, $SE = 0.07$; PBO $M = 1.85$, $SE = 0.08$) or second (C-CT $M = 1.86$, $SE = 0.07$; FLX $M = 1.80$, $SE = 0.07$; PBO $M = 1.75$, $SE = 0.09$) years of follow-up ($ps > .30$, two-tailed).

Discussion

We examined stable remission, recovery, and continuous symptom levels among outpatients with recurrent MDD who (a) responded to acute phase CT but were at higher risk for relapse, (b) were randomized to 8 months of depression-specific continuation phase treatment (C-CT or FLX) or PBO, and (c) were assessed for 24 additional months (Jarrett & Thase, 2010). Unstable remission during acute phase CT (specifically, any of the last 7 acute-phase HRSD scores ≥ 7) defined higher risk among randomized patients. We employed rigorous, longitudinal definitions of stable remission and recovery: 6 weeks and 8 months, respectively, of minimal or absent depressive symptoms post-randomization. Among 241 randomized patients, 68% and 47% were observed to have stable remission and recovery, respectively, within 32 months after acute phase CT. However, some patients likely had unobserved stable remission and recovery because they dropped out of the study or were censored at the point of relapse (after which they were referred outside the study protocol for treatment). Consequently, we also computed actuarial estimates that are generally regarded as more accurate than raw proportions (e.g., Singer & Willett, 2003). Actuarial estimates were that most patients remitted (97%) and recovered (94%) within 32 months. Neither observed nor estimated proportions of patients remitting or recovering varied significantly among CCT, FLX, or PBO arms at 8, 20, or 32 months (i.e., after the experimental phase and 1 and 2 years of follow-up), failing to support our first hypothesis.

In contrast, a previous randomized trial of C-CT versus assessment-only control did find significantly more recovery (but not stable remission) with C-CT among responders at both higher and lower risk after acute-phase CT (Vittengl et al., 2009). Stable remission and recovery in the current C-CT arm were similar to those in the previous trial at 24 months post-randomization. However, recovery in the current PBO arm significantly exceeded recovery in the previous assessment control group. This difference is especially noteworthy because the previous trial included both lower and higher risk acute phase CT responders, which may have increased recovery compared to the current trial with only higher risk responders. Consequently, the lack of greater recovery with C-CT versus PBO in the current trial may be due to patients benefitting from PBO relative to assessment only. We speculate that the two control conditions are distinguished by expectancies such that double-blinded PBO is a credible control (i.e., patients and clinicians believe that FLX may be provided) compared to an assessment-only control, in which there is no active treatment possibility. Consistent with this possibility, the current C-CT group matched the previous C-CT group and significantly exceeded the previous assessment-only control group in recovery (Vittengl et al., 2009).

Analysis of continuous residual symptom scores supported our second hypothesis. On average, patients had mild depressive symptoms that decreased slightly from the experimental phase (0-8 months after randomization) to the first (9-20 months) and second (21-32 months) years of follow-up. During the experimental phase, patients randomized to C-CT and FLX showed significantly lower symptoms (about 0.21-.0.25 *SD*) compared to patients receiving PBO, in analyses using all available data (e.g., including after relapse) and accounting for non-protocol treatment. The C-CT and FLX groups did not differ significantly, suggesting that they are about equally effective in maintaining low depressive

symptoms among higher-risk responders to acute phase CT. In addition, differences between the three experimental groups were not significant during follow-up, suggesting that benefits of C-CT and FLX may not endure long after treatment discontinuation, and/or the benefits of responding to acute phase CT continue to endure at some level for higher-risk responders after discontinuation of depression-specific treatment. The primary analysis of the current trial that focused on prevention of relapse and recurrence (Jarrett et al., 2013) concluded similarly that C-CT and FLX both reduced relapse compared to PBO during the experimental phase, but not after discontinuation of treatment.

Among higher-risk responders to acute phase CT for recurrent MDD, we found that positive outcomes (stable remission and recovery) were empirically, as well as conceptually, distinct from the absence of negative outcomes (relapse and recurrence). Stable remission did not correlate significantly, and recovery correlated statistically significantly but modestly, with the absence of relapse and recurrence. For example, the presence of a positive event did not guarantee freedom from a later negative outcome—about a third of patients who remitted, and a fifth of those who recovered, later relapsed or recurred by the end of the 32-month assessment period. On other hand, the *absence* of a positive event nearly guaranteed subsequent relapse in the current sample (96% and 97% of patients who failed to remit and recover, respectively, later relapsed), and only one patient experienced none of these events (stable remission, recovery, relapse, or recurrence). These results largely replicate a previous clinical trial (Vittengl et al., 2009) and highlight the value of studying stable remission and recovery in addition to relapse and recurrence among patients with MDD.

Although the prior randomized trial of C-CT (Jarrett et al., 2001; Vittengl et al., 2009) is more closely comparable, the current results also are interpretable among other related studies. For example, studies of continuation and maintenance CT vs. pharmacotherapy (Blackburn & Moore, 1997), and CT plus pharmacotherapy versus pharmacotherapy alone (Paykel et al., 1999), have shown no differences between these treatments' effects on residual depressive symptoms. However, maintenance CT has been shown to reduce residual symptoms compared to assessment-control (Klein et al., 2004). These results parallel our findings of no significant difference between FLX and C-CT, with each superior to PBO, in reducing residual symptoms during the continuation phase. However, individual differences in patients' demographic and clinical histories, as well as psychosocial functioning, may moderate continuation treatments' effects (Vittengl, Clark, & Jarrett, 2010; Vittengl, Clark, Thase, & Jarrett, under review).

Prior studies' results for remission and recovery are more variable, highlighting potential differences due to variation in samples, treatments, outcome definitions, and methods of estimation. For example, Fava et al. (2004) reported that after 6 and 12 months, 100% and 85% of continuation CT patients, and 100% and 55% of clinical management patients, respectively, were in remission (i.e., had minimal or absent symptoms at the time of assessment). These high remission rates parallel the current results, although Fava et al. (2004) focused on loss of remission, whereas we estimated gain of remission. Also similar to our high actuarial estimates of recovery, Curry et al. (2011) found that recovery (defined as 8 weeks of normal-range depressive symptoms) within 24 months was common (96%) among adolescents with MDD who responded to one of four short-term treatments (CT,

FLX, PBO, or combined CT and FLX), and did not differ among treatments. On the other hand, other research has yielded less remission (within 20 weeks, 24% remitted with continuation/maintenance CT plus pharmacotherapy vs. 11% with pharmacotherapy alone, when remission was defined as HRSD < 8 and BDI < 9 for 4 weeks; Paykel et al., 1999) and recovery (within 2 years, 26% recovered with maintenance pharmacotherapy vs. 19% with placebo, when recovery was defined as HRSD ≤ 3 for ≥ 120 days; Dunlop et al., 2012).

Qualities of our sample, procedure, and measures may limit the generalizability of our findings. For example, selected patients had carefully diagnosed recurrent MDD and received CT from proficient, supervised therapists who demonstrated competence in CT and followed a standardized treatment protocol. Variations in patients, therapists, and CT may produce different outcomes. Further, our definitions and assessment of stable remission and recovery were more rigorous than has been common historically in depression research. For example if cross-sectional (e.g., low symptoms during the 35th week after acute-phase treatment discontinuation) rather than our longitudinal (e.g., low symptoms during all weeks 1-35 to define recovery) assessment methods were used, remission and recovery estimates might be higher. Finally, greater censoring of patients from the medication groups (PBO and FLX) possibly decreased the apparent benefit of C-CT in our analyses. Similarly, although the C-CT arms yielded similar proportion of stable remission and recovery, there was some evidence that patients benefitted from the credible control, PBO, compared to the assessment-only arm of a previous C-CT trial (Vittengl et al., 2009). The sources of apparent benefits of the PBO condition are unknown but likely included some combination of patients' positive expectancies about the pills they received plus regular discussion of symptoms and non-specific support from pharmacotherapists.

The current results have several clinical implications. First, our results strengthen the evidence base for *acute-phase* CT because a substantial proportion of high risk responders experienced extended periods of minimal or absent symptoms (stable remission and recovery), with (C-CT or FLX) and without (PBO) continued depression-specific treatment. Second, our results highlight the episodic nature of MDD because many patients who remitted and/or recovered later experienced return of major depression, and nearly all patients who failed to remit and/or recover later relapsed. Third, the current results extend the evidence base for C-CT. To our knowledge, the current randomized trial is the first to compare C-CT, FLX, and PBO for higher-risk responders to acute phase CT. The depression-specific treatments (C-CT and FLX) were about equally helpful in maintaining lower depressive symptoms compared to PBO (and also in preventing relapse, Jarrett et al., 2013), but only as long as continuation treatment was active. Consequently, longer courses of continuation and/or maintenance treatments may be indicated for patients with recurrent MDD to control residual symptoms (e.g., Fava & Tomba, 2010; Zajecka, Kornstein, & Blier, 2013). Thus, the current findings reflect incremental progress toward understanding what constitutes sufficient treatment for recurrent MDD, and highlight not only the pernicious qualities of this illness, but also the necessity of improving treatments, for example, by increasing effectiveness or delivering efficacious treatments in more effective durations or sequences.

Acknowledgments

This report was supported by Grants Number K24 MH001571, R01 MH58397, R01 MH69619 (to Robin B. Jarrett, PhD) and R01 MH58356 and R01 MH69618 (to Michael E. Thase, MD) from the National Institute of Mental Health (NIMH). We appreciate the support of our NIMH Program Officer, Jane Pearson, PhD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIMH or the National Institutes of Health. We also appreciate the careful review by members of the trial's Data Safety and Monitoring Board. We are indebted to our research teams and our colleagues at The University of Texas Southwestern Medical Center at Dallas, the University of Pittsburgh (where Dr. Thase was located during patient accrual), and the University of Pennsylvania (Dr. Thase's current affiliation). We appreciate the assistance of Abu Minhajuddin, PhD, in preparing this manuscript.

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**Outcomes of Patients who Responded to Acute Phase Cognitive Therapy
(A-CT) for Depression over 32 Months**

Figure 1.

The numbers inside the boxes reflect the number of patients who experienced each event. Arrows show the progression events within 32 months after discontinuation of A-CT.

Figure 2.

Estimated probabilities of stable remission (6 weeks of consistently minimal or absent depressive symptoms) were derived from Cox regression analyses. The continuation phase cognitive therapy and pill placebo lines are nearly fully overlapping. Patients were censored before stable remission when they relapsed (and were referred for non-protocol treatment) or dropped out. Through the end of follow-up, the three groups did not differ in time to stable remission, $\chi^2(2) = 0.95$, $p = .62$.

Figure 3.

Estimated probabilities of recovery (8 months of consistently minimal or absent depressive symptoms) were derived from Cox regression analyses. Patients were censored before recovery when they relapsed (and were referred for non-protocol treatment) or dropped out. Through the end of follow-up, the three groups did not differ in time to recovery, $\chi^2(2) = 3.99$, $p = .14$.

Figure 4.

Estimated means were derived from a repeated-measures multilevel model controlling non-protocol treatment. Weekly mean Psychiatric Status Ratings are in the range of 1 (no depressive symptoms), 2 (one or two mild symptoms), and 3 (obvious symptoms with moderate impairment but does not meet criteria for major depressive disorder).

Table 1

Observed Proportions of Patients Remitting and Recovering by Selected Time Points

Outcome	Experimental Condition			Between Conditions	
	C-CT (<i>n</i> = 86)	FLX (<i>n</i> = 86)	PBO (<i>n</i> = 69)	Pearson $\chi^2(2)$	<i>p</i>
Stable remission					
8 months	.72 (.61, .81)	.71 (.60, .80)	.58 (.45, .70)	4.15	.13
20 months	.73 (.63, .82)	.73 (.63, .82)	.59 (.47, .71)	4.43	.11
32 months	.74 (.64, .83)	.73 (.63, .82)	.59 (.47, .71)	4.87	.09
Recovery					
8 months	.30 (.21, .41)	.26 (.17, .36)	.16 (.08, .27)	4.31	.12
20 months	.50 (.39, .61)	.48 (.37, .59)	.36 (.25, .49)	3.25	.20
32 months	.51 (.40, .62)	.50 (.39, .61)	.38 (.26, .49)	3.31	.19

Note. Numbers in parentheses designate the 95% confidence interval. After responding to acute phase cognitive therapy, patients received 8 months of continuation phase cognitive therapy (C-CT), or Clinical Management plus either double-blinded fluoxetine (FLX) or pill placebo (PBO) and were followed 24 additional months. Months are since randomization to experimental conditions.

Table 2

Cox Regression Estimated Proportions of Patients Remitting and Recovering by Selected Time Points

Outcome	Experimental Condition			Between Conditions	
	C-CT (<i>n</i> = 86)	FLX (<i>n</i> = 86)	PBO (<i>n</i> = 69)	Likelihood Ratio $\chi^2(2)$	<i>p</i>
Stable remission					
8 months	.87 (.74, .93)	.90 (.78, .95)	.86 (.71, .93)	0.72	.70
20 months	.94 (.81, .98)	.96 (.86, .99)	.94 (.79, .98)	0.95	.62
32 months	.96 (.84, .99)	.98 (.87, 1.00)	.96 (.80, .99)	0.95	.62
Recovery					
8 months	.38 (.26, .48)	.35 (.22, .45)	.24 (.11, .36)	2.37	.31
20 months	.88 (.74, .94)	.90 (.77, .96)	.76 (.56, .87)	3.96	.14
32 months	.94 (.81, .98)	.96 (.85, .99)	.87 (.64, .95)	3.99	.14

Note. Estimates derived from Cox regression analyses accounting for censoring of patients at relapse and drop from the longitudinal study before remission and recovery. Numbers in parentheses designate the 95% confidence interval. After responding to acute phase cognitive therapy, patients received 8 months of continuation phase cognitive therapy (C-CT), or Clinical Management plus either double-blinded fluoxetine (FLX) or pill placebo and were followed 24 additional months. Months are since randomization to experimental conditions.